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Effect of vitamin A deficiency on anaphylaxis in the guinea pig

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THE EFFECT OF VITAMIN A DEFICIENCY ON ANAPHYLAXIS IN THE GUINEA PIG

by

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INTRODUCTION

CHAPTER I

Allergy has in recent years acquired an important place in medicine. Naturally this has increased the amount of experimentation on allergy. Part of this work has been accomplished by studying anaphylaxis in the guinea pig. Since allergy occurs in otherwise seemingly healthy individuals, the question as to why one person should be allergic and another not is important. The same situation occurs in guinea pigs. In a litter of animals it may be possible to sensitize only a part of them (24). The part that vitamin deficiency plays in allergy has only recently been investigated. The effect of vitamin A deficiency on anaphylaxis in the guinea pig is a continuation of this study.

Hypersensitiveness has been defined (5) as the specific susceptibility to a substance which ordinarily is harmless to normal individuals. This state results from exposure either by administration of, or by contact with, the offending substance. The state which occurs in animals of increased susceptibility to repeated injections of a foreign protein is termed anaphylaxis (9a). Hypersensitiveness, depending entirely upon qualitative differences among humans, is called allergy (4).

Anaphylaxis

Only since the beginning of the twentieth century has the phenomenon of anaphylaxis been studied. In 1902, Portier and Richet, the first to name and study carefully anaphylaxis, published their report (9b). Since that time much theorizing has been done on the mechanism of the anaphylactic shock. From the following facts it appears almost certain that the interaction of the antigen and antibody takes place at the cells of the sensitive tissue (5).

1. There is an incubation period necessary for active sensitization. This has been interpreted as the time necessary for the formation and attachment of the antibody to the tissue.

2. In passive sensitization there is a latent period of from four to six hours after the injection of the sensitized serum before anaphylactic shock can be induced in the animal.

3. If one injects a mixture of the harmful protein and its antibody there is no reaction.

4. If 90% of the blood of a sensitive guinea pig is replaced by that from a nonsensitive pig, one can still induce shock.

5. The uterine strip of a sensitive guinea pig responds when placed in a solution of the specific protein.

This reaction is known as the Schulz-Dale reaction.

The actual site of the reaction has not yet been established. It was first thought to be the central nervous system but this was disproved by the positive reaction to anaphylactic shock in decerebrated and pithed, sensitive animals. There is evidence that both the capillary endothelium and the smooth muscle participate in anaphylactic shock (9d).

Two of the many theories on the mechanism of the anaphylactic shock are presented here. The chemical theory is based on assumption of a liberation of a toxin-like substance from the cells, caused by the interaction of the antigen and antibody. It is believed by some that this toxin-like substance is histamine or a histamine-like substance (5). Histamine has been found present in all the organs thus far studied. The injection of histamine into a non-sensitive animal produces the same symptoms as does an anaphylactic shock. Also supporting the chemical theory is the fact that the blood of a guinea pig in the state of anaphylactic shock is toxic for a nonsensitive guinea pig.

The second theory, the physical theory, states that the union of the antigen and antibody results in a disturbance of the colloidal equilibrium of the plasma or cell protoplasm. This theory is supported by the Schulz-Dale reaction. In the cellular theory it is a question as to

why all the local histamine, or histamine-like substances are not exhausted (9e).

The shock in anaphylaxis produces characteristic symptoms differing with species. In the guinea pig this also varies with the route of injection (9b). Within a minute after intravenous injection of the specific foreign protein, the sensitized animal shows distress. The hair on the head and back of the neck becomes ruffled. The animal is restless, coughs and retches. It rubs its nose and seems to choke. The respiration rate is first increased and then decreased and becomes labored. This is followed by defecation and urination. If a fatal does of the antigen is given the animal becomes weak, falls on its side, goes into convulsions and finally dies. Death may occur within five minutes after the injection. At autopsy the lungs show a uniform emphysema filling the pleural cavities. Histologically the bronchioles are contracted and the mucosa much folded. In delayed death multiple petichial hemorrhages are found in the organs.

Rosenau and Anderson working in 1906 (25) found that guinea pigs could be sensitized by feeding. The animals were tested by inoculation. In one group of guinea pigs which were fed a mixture of dried carrots and horse serum and tested ten to fourteen days later, all animals reacted positively. In the report of their work they gave no account

of the previous diet of their animals. Their work confirmed that of Uhlenhuth and Metalnikoff who also said nothing about the diets they used previous to the experimental work (25). The work of Rosenau and Anderson has been considered classical but it is now questioned as to whether or not their diets were adequate.

Allergy

Allergy is more common than is generally supposed. All persons are potentially allergic but vary widely in degree in response to a harmful environment (22). It has been estimated that as many as 7% of the people in the United States are naturally allergic (90). Allergy in man is often more than specifically selective for he can also be sensitized by physical agents (6). Food hypersensitiveness is most common in early childhood and in many cases is gradually lost. Sensitization to inhalents is rare in infancy and increases rapidly between the ages of three and eight. This allergy is often acquired and tends to be permanent, while there is more evidence that the susceptibility to food allergy is inherited (3).

The pathology of human hypersensitiveness consists of edema of the mucous membranes and the skin. Occasionally hemorrhage may be present such as in essential hematuria. In lesions such as dermatitis it may consist of inflamation

of the skin. Eosinophils are found in increasing numbers not only in the affected tissue but also in secretions such as in the nasal secretions of nasal allergy. In food allergy the clinical manifestations consist of canker sores, acute gastero-enteritis and certain types of mucous colitis. (5)

Allergy to food may cause any number of symptoms (26). Abdominal symptoms may consist of pain, colic, gastric and intestinal distress, distension, nausea, vomiting, constipation or diarrhea. Urticaria is the sole manifestation in 75% of the patients. Eczema, certain migraines, and bronchial asthma are common manifestations of food allergy. A typical case of food allergy shows a combination of symptoms such as is present in the cases quoted from Walzer (33).

"J. M., female, five years old, was admitted in January, 1926, with a history of asthma of one year's duration. She had had eczema at the age of three months..... Asthmatic attacks started at the age of four, usually followed by acute bronchitis. Since she was one year old, mere contact with fish would cause a severe diffuse urticaria.

L. G., male, two years old, was admitted in September, 1925, with a history of eczema, urticaria, and asthma starting at the age of four months. Patient's mother and aunt are both sensitive to fish. Eczema started at four months and persists to the present time..... On the only occasion when fish was ever given, the mother states that it resulted in a severe "coughing spell", a rise in temperature and diarrhea."

The second case is also of interest because of the picture of inheritance of a predisposition to allergy.

One of the causes of food allergy is the faulty digestion of protein, with the consequent absorption of it in

an undigested state (19). However, Walzer (32) reports that out of 50 people, passively sensitized by intradermal injection of blood from very sensitive people, only six people failed to react positively (wheal, burning, and itching at the site of injection). Sensitization of the nursling apparently does occur through the foreign protein ingested with the breast milk. The foreign protein even though absorbed by the mother does not sensitize the mother (19). However it is not to be surmised that a large part of the ingested protein is absorbed in an undigested state. Walzer (33) believes that the permeability of the gasterointestinal canal is normal, not unusual. Hammarsten's (11) view is that absorption of undigested protein takes place only under certain unusual conditions which are (1) extraordinary permeability of the intestinal wall as in the new born, (2) lessened activity of the digestive enzymes, and (3) a flooding of a portion of the alimentary canal with protein. The flooding of the alimentary track increases the stasis in which condition active peristalsis may be observed. This increases the pressure which is an essential factor for absorption (13).

Other causes for the allergic phenomenon besides the absorption of undigested protein have been studied. The chemical constituents of the blood have been investigated rather thoroughly (22). The cholesterol content and also magnesium, calcium and phosphorus contents of the blood of

allergic people are normal. The potassium content of the skin is lost by irritation in allergic individuals and the injection of potassium salts has about the same effect as that of epinephrine. Epinephrine increases the potassium salts of the blood.

The medical profession accepts two groups of allergies (4): One in which are put the normal forms dependent only upon quantitative variations within the species is exemplified by serum sickness and dermatitis venenata. The second group includes the abnormal forms dependent entirely upon qualitative differences within the species. This group is termed atopy or natural or inherited allergy (5). It is characterized by a strong hereditary factor and is usually based upon a specific immunological mechanism. An atopic individual inherits a predisposition to a sensitive shock tissue as well as the ability to produce reagins or antibodies following a suitable exposure. Food allergy falls in the class of atopy.

Anaphylaxis and Allergy Compared

In the comparison of anaphylaxis and allergy the greatest difficulty lies in the fact that so little is known about the allergic antigen or "allergin". It is a question as to whether or not the allergin is antigenic, but in most cases it has proved to be. The anaphylactenogens are anti-

genic (9f). The second point of comparison, that animals may be sensitized in the same manner as humans may, has been more difficult to prove. It has been possible to sensitize guinea pigs by their inhaling and also by their eating the antigen. The biggest difference between allergy and anaphylaxis occurs in the inheritable nature of the former. It has been found however that inheritance explains why some individuals of a species of animals are refractory to sensitization while others are not. Emphasis has been placed upon the fact that one can only irregularly passively sensitize the skin of a normal animal, by the serum of a sensitive person. This cause for differentiation of the phenomena has proved to be unfounded for sensitivity in general can not be passed from one species to another (36). Complete desensitization which is possible in anaphylaxis is not always possible in allergy because of the inability to always determine the true antigen (5).

Vitamin A

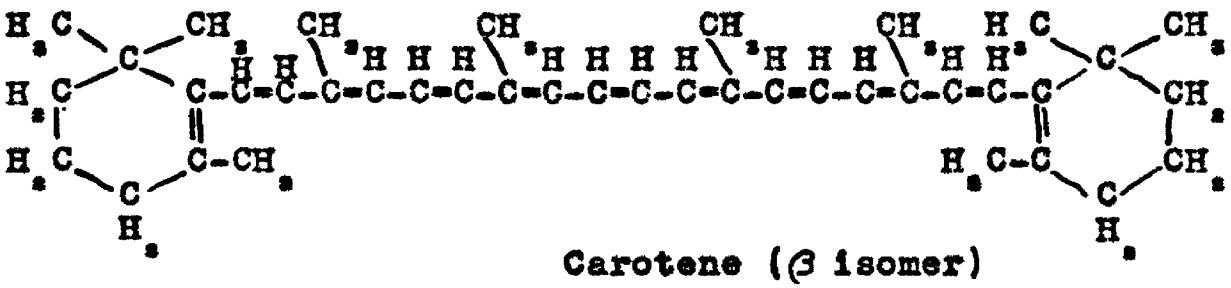
Vitamin A deficiency has been observed among people for a long time. Hippocrates was among the first to describe nightblindness. Before the World War it was prevalent in Russia during the Lenten fasts (14).

Until the end of the first decade of the present century the teaching concerning nutritional needs of the

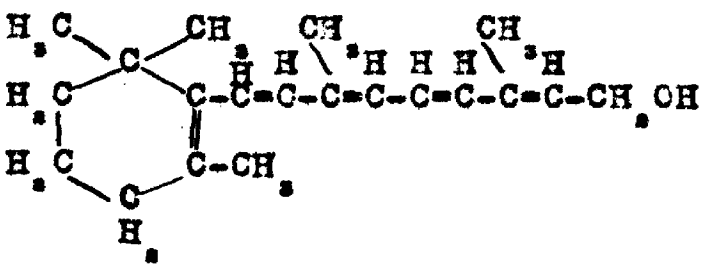
human being was based on calories and proteins. Besides carbohydrates, fats and proteins, a few minerals were also considered important. In 1911 the results of animal experimentation showed the necessity of "vitamines". This name, because of the lack of relationship to amines has been changed to vitamin (15).

A characteristic of each vitamin is the very small amount in which it exercises its physiological functions.

In 1914 McCollum and Davis extracted a fat soluble vitamin from butter which they termed "fat soluble A". (7) In 1919 Steenbock suggested the relationship of vitamin A to carotene. This relationship may be seen from the following formulae (1).



Carotene (β isomer)



Vitamin A

There is considerable disagreement as to the present day prevalence of vitamin A deficiency in people. It has been reported that as high as 16% of the people of the Netherlands are deficient in vitamin A (10). Certainly in this country nightblindness and xeropthalmia are not prevalent but these symptoms are late manifestations of vitamin A deficiency (35). Fishbein (8) reports that there are many more cases of vitamin A deficiency than commonly supposed, that this is shown up in the many instances of malaise among people. Jeans and Zentmire in testing school children found from 25-75% of different social groups giving evidence of insufficient vitamin A (16). A biophotometer was used for measuring the deficiency. This equipment is not generally accepted as a reliable means for testing vitamin A deficiency.

The result of vitamin A deficiency is the change in the epithelial tissue. The epithelium is atrophied causing inertness in the physiological activities and in its role of covering membranes. This change is called keratinizing metaplasia. The sequence in the pathology is interesting. A break in the continuity of a tissue, instead of being repaired normally, is followed by a proliferation of the basal cells. These cells respond by active mitotic division and replace the original cells which are usually columnar or cuboidal in type by squamous cells. In the human the tissue replaced by the keratinizing metaplasia is, in sequence,

the conjunctiva, the mucosa of the nares, the accessory sinuses, the trachei and bronchii, and the pancreas, renal pelvis, ureters, salivary glands and uterus (34). The secondary effects are loss of weight due to fat loss, anemia, cessation of growth of bones, and degenerative lesions of the skeletal muscles. Mellanby also reports that a vitamin A deficiency causes degenerative changes in the central nervous system, especially in the cord (18).

The deficiency of vitamin A seems to depress the anacidity of the stomach (21). It is a question as to whether or not a deficiency has any effect upon protein, fat and carbohydrate metabolism. It is thought to have some effect upon that of carbohydrates (10). Vitamin A deficiency plays a part in the susceptibility to infection. It is easier for an organism to gain entrance through already pathological tissue (2).

Vitamin A deficiency shows essentially the same manifestations in lower animals as it does in human beings. Rats have long been used for standardizing vitamin A (2). Only recently, however, has xeroptholmia been shown in the monkey and the guinea pig (12). Storage of reserve vitamin A in the tissue, the non-resistance to infection during the depletion period and inadequate diets may have been causes for the previous failures.

Avitaminoses, Anaphylaxis and Allergy

Sereni studying avitaminoses and anaphylaxis in the guinea pig found that, in experiments on passive sensitization, guinea pigs deficient in vitamin C showed a much greater shock than did normal animals (27). Later (28) working with actively sensitized pigs he found that the deficient animals again showed greater shock than the controls. He concluded that avitaminoses increases the susceptibility to the agent causing anaphylaxis and that a delayed production of antibodies may also be involved.

Vitamin C deficiency (3) has been shown to increase the susceptibility to shock when the antigen is fed to guinea pigs. Animals could also be sensitized by feeding if they were deficient. This raises the question as to whether or not Rosenau's and Anderson's pigs had had adequate diets before they were sensitized by feeding.

Vitamin C also plays a part in food allergies. In seven patients (22) who were found deficient in vitamin C and suffering from urticaria, with the addition of vitamin C to the diet, the urticaria subsided.

Viosterol of high potency given in massive doses to patients having urticaria, chronic asthma and seasonal hay fever, had no effect on the first two allergies, but protected all the hay fever patients to some degree during the season (22).

The effect of avitaminoses A on allergy is unknown but the results of this paper show the effect on anaphylaxis. The effect of vitamin C deficiency on anaphylaxis (3) suggested the problem of the effect of vitamin A deficiency. The destruction of the epithelium and replacement of it by keratinized tissue has raised the question as to whether or not the intestine in vitamin A deficient animals is not more permeable to undigested proteins than that of animals which are not deficient. The effect of an increase of vitamin A in the diet of allergic people is still unknown.

EXPERIMENTAL

CHAPTER II

The experimental animals used were young female guinea pigs weighing from 250 to 350 gms. Young animals were chosen because of their being more easily depleted of vitamin A. The animals were divided into four groups; groups I and III being experimental animals, groups II and IV being controls. The guinea pigs were kept in cages having false bottoms so that the urine and feces fell through. Five animals were placed in each cage.

The guinea pigs were fed the same diet as that used in the experiments on vitamin C deficiency (3). The diet consisted of a mixture of rolled oats: 2300 gms., powdered skim milk: 600 gms., McCollum's salt mixture 185: 60 gms., sodium chloride: 30 gms. In the beginning the powdered skim milk was refluxed with 95% ethyl alcohol for 2 hours, filtered while hot and dried, in order to remove any remaining vitamin A (20). This procedure was found to be unnecessary as the animals became depleted almost as readily when fed untreated powdered skim milk. The diet was mixed thoroughly with water and dried. This mixture was fed ad lib. Vitamin C was supplied to all animals by the injection of .5 c.c. of a solution of cevitamic acid containing 12 mg. per c.c. and neutralized with sodium hydroxide. Every animal received two drops of viosterol every third day. Groups II and IV

were given three drops of carotene in oil every other day.

Two methods of sensitization were used. Groups I and II were sensitized by the injection intraperitoneally of 1 c.c. of a 1-10 dilution of egg white every third day for three times. Groups III and IV were sensitized by feeding them a mixture of the regular diet: 1500 gms., and egg white 700 c.c.s for four days. This was fed ad lib. After the feeding of this mixture Group IV was depleted of vitamin A.

Animals were tested for the anaphylactic shock reaction by feeding them 10 c.c. of a mixture of egg white, 1 part and tomato juice 3 parts. The tomato juice was added to make it palatable. The guinea pigs were starved for twenty-four hours previous to feeding. They were not tested less than three weeks after sensitization.

Group II consisting of animals sensitized by injection were tested when not deficient in vitamin A and when deficient in vitamin A.

RESULTS

CHAPTER III

Table I shows the results of the testing of Group I for anaphylactic symptoms. These animals were depleted of vitamin A and sensitized by injection. From the table it will be seen that all animals showed some signs of shock. All, except two of the animals which died of vitamin A deficiency, were tested a second time a week later. They again responded to the feeding with shock symptoms. Only two of the animals, nos. 25 and 28, had convulsions and this occurred after feeding them about three c.c.s of the tomato juice-egg white mixture. No animals in this group died from shock.

Group II, Table II, was the control group for Group I. As can be seen from the table only one animal, number 31, responded to the tomato juice-egg white mixture and this response was but slight. Though the others were tested twice there was no sign of shock among any of them.

In Group I it will be noted that there were two animals which showed a mild shock, two a medium shock and two a severe shock. Group II showed one animal having a mild shock and eight having no reaction.

Table III represents the results of the feeding of Group II after the animals were depleted of vitamin A. Every animal responded to the feeding. One guinea pig, number 37,

had severe convulsions but recovered. Another, number 33, showed a paralysis of the hind legs and also convulsions. This animal also recovered. Guinea pig number 39 had severe convulsions and died about seven hours after feeding. This group showed three animals having a severe shock, two a medium one and two a mild one.

Tables IV and V give the results of the feeding of what was left of Groups III and IV. Most of the animals of these groups died from vitamin A deficiency before it was possible to test them. From Table IV it will be seen that both animals responded positively to the feeding. Group IV showed one animal with positive symptoms and one with negative symptoms.

In autopsy of animals which showed shock symptoms, characteristic changes were found. Petichial hemorrhages of the intestine were common. The stomach was inflated and hemorrhaged. Other changes were found but these were not consistant with all animals.

Table I

Group I. Animals sensitized by injection; tested by feeding when deficient in vitamin A.

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
20	280	1st shock 52 days after sensitization and beginning of diet.	290	Dyspnea, ruffled coat, scratched nose and belly. Died three days later of vitamin A deficiency.
23	220	1st shock 52 days after sensitization and beginning of diet.	260	Dyspnea, ruffled coat, scratched nose.
		2nd shock 59 days after sensitization and beginning of diet.	295	Bit belly, ruffled coat, scratched nose, dyspnea, cough.
25	270	1st shock 52 days after sensitization and beginning of diet.	305	Dyspnea, ruffled coat, scratched nose and belly.
		2nd shock 59 days after sensitization and beginning of diet.	315	Convulsions, urination. Recovered.
26	350	Shock 52 days after sensitization and beginning of diet.	320	Rubbed nose immediately. Severe dyspnea coughed. Died four days later of vitamin A deficiency.

Table I Continued

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
28	290	1st shock 52 days after sensitization and beginning of diet.	350	Convulsions. Recovered.
		2nd shock 59 days after sensitization and beginning of diet.	335	Dyspnea, rubbed nose.
30	370	1st shock 52 days after sensitization and beginning of diet.	405	Little dyspnea, bit belly, scratched nose.
		2nd shock 59 days after sensitization and beginning of diet.	415	Ruffled coat, severe dyspnea, bit belly, scratched nose.

Table II

Group II. Control animals for Group I, sensitized by injected, tested by feeding when not deficient in vitamin A.

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
31	290	1st shock 52 days after sensitization.	300	Slight dyspnea, rubbed nose.
		2nd shock 59 days after sensitization.	310	None
32	240	1st shock 52 days after sensitization.	255	None
		2nd shock 59 days after sensitization.	280	None
33	260	1st shock 52 days after sensitization.	400	None
		2nd shock 59 days after sensitization.	415	None
35	360	1st shock 52 days after sensitization.	380	None
36	320	1st shock 52 days after sensitization.	340	None
		2nd shock 59 days after sensitization.	360	None
37	350	1st shock 52 days after sensitization.	415	None
		2nd shock 59 days after sensitization.	455	None

Table II Continued

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
38	350	1st shock 52 days after sensitization.	365	None
		2nd shock 59 days after sensitization.	380	None
39	290	1st shock 52 days after sensitization.	305	None
		2nd shock 59 days after sensitization.	330	None.

Table III

Original Group II. Tested as shown in Table II. Tested again by feeding when deficient in vitamin A.

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
31	370	50 days after beginning of diet, 109 days after sensitization.	380	Severe dyspnea, bit belly, scratched nose.
33	260	50 days after beginning of diet, 109 days after sensitization.	430	Convulsions, hind legs paralized. Recovered
35	360	50 days after beginning of diet, 109 days after sensitization.	335	Dyspnea, rubbed nose, coughed, bit belly.
36	350	50 days after beginning of diet, 109 days after sensitization.	305	Dyspnea, coughed.
37	350	50 days after beginning of diet, 109 days after sensitization.	325	Convulsions, recovered.
38	350	50 days after beginning of diet, 109 days after sensitization.	380	Dyspnea, rubbed nose.

Table III Continued

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
39	290	30 days after beginning of diet, 109 days after sensitization.	300	Convulsions, died seven days after shock.

Guinea pig no. 32 died of vitamin A deficiency.

Table IV

Group III. Animals sensitized by feeding when deficient in vitamin A, tested by feeding when deficient in vitamin A.

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
4	240	Shocked 30 days after sensitization and 70 days after beginning of diet.	355	Dyspnea, rubbed nose, ruffled coat.
6	300	Shocked 30 days after sensitization and 70 days after beginning of diet.	320	Dyspnea, ruffled coat, coughed. bit belly, rubbed nose.

Table V

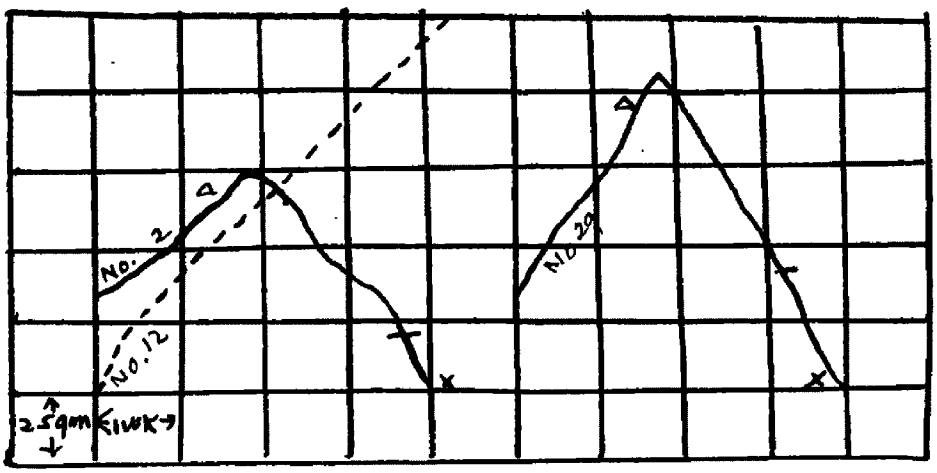
Group IV. Controls for Group III, feed antigen when not deficient in vitamin A, tested by feeding when deficient in vitamin A.

Guinea Pig No.	Initial Weight	Shock	Final Weight	Shock Symptoms
17	330	Shocked 68 days after beginning of diet and sensitization.	350	Slight dyspnea, coughed, rubbed nose.
16	350	Shocked 68 days after beginning of diet and sensitization.	450	None

DISCUSSION

CHAPTER IV

The experimental work offered a good opportunity to study vitamin A deficiency in the guinea pig. All animals that weredeficient with the possible exception of two (control animals which will be discussed later) showed keratinization of the cornea of the eye. Breathing in all cases of deficient animals was labored and loud indicating that the mucosa of the lungs was keratinized. Weight decreased rapidly, as may be seen from the graph below. This was probably due to loss of fatty tissue and loss of appetite.



Graph I
Weight curves of two typical animals deficient in vitamin A and of one typical animal not deficient.

Δ = keratinization of eyes _____ = deficient animals
– = protrusion of intestines ----- = non-deficient animals
x = death

All the animals deficient in vitamin A and sensitized by injection had shock symptoms when fed the tomato juice and egg white. This indicates that in a vitamin A deficient animal the intestine becomes more permeable than that of a normal animal to undigested proteins.(3) The animals which had a diet with a high carotene content were essentially negative to the test for permeability of the intestine. In the group of animals sensitized by feeding only one animal had positive shock symptoms. The intestines of the animals with a high vitamin A content in their diet certainly were much less permeable to the protein than those of vitamin A deficient animals.

Two animals that were deficient in vitamin A and one that supposedly wasn't were sensitized by feeding egg white mixed with the diet. It was impossible to sensitize a fourth animal that wasn't deficient. The three animals sensitized by feeding responded by shock to a later feeding.

Two control animals that were supposedly not deficient in vitamin A gave positive results to the shock test. From the weights of the animals it can be seen that they were poorly nourished. That all animals do not absorb carotene as readily as others is also an important factor. The experimental animals were a heterogenious stock and these two animals may have been unable to absorb the carotene.

The animals that were deficient in vitamin A did not

respond with as severe a shock as did those deficient in vitamin C reported by Bronfenbrenner et al. Only one animal deficient in vitamin A died from shock and that was a delayed death while 90% of those deficient in vitamin C died of shock immediately. Vitamin A apparently does not play as big a role in the permeability of the intestine as does vitamin C, but it does play an important part.

SUMMARY AND CONCLUSIONS

CHAPTER V

1. The effect of vitamin A deficiency on anaphylaxis in the guinea pig has been studied.
2. The gross pathology of vitamin A deficiency in the guinea pig has been observed.
3. It was found that vitamin A deficiency made possible the shocking of a sensitized guinea pig by feeding the anaphylactenogen. Animals not deficient could not be shocked this way.
4. It has been indicated that it is possible to sensitize guinea pigs deficient in vitamin A by feeding, and that it is more difficult to sensitize animals which are not deficient by this method.
5. It is suggested that vitamin A deficiency may play a definite though prehaps slight part in food allergy.

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